UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

February 8, 2013
TXR # 0056430

SUBJECT: Tau-Fluvalinate: Summary of Hazard and Science Policy Council (HASPOC) Meeting of August 2, 2012: Recommendations on the need for sub-chronic inhalation and 90-day dermal toxicity studies.

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MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jess Rowland, Ray Kent,

Other Attendees: Julie Van Alstine, Kristin Rury

Presenter: William Irwin, Ana Rivera Lupianez

I. PURPOSE OF MEETINGS:

Based on current policies, a subchronic inhalation toxicity study is required for tau-fluvalinate due to the potential for repeated handler inhalation exposure anticipated from use on agricultural crops. Under the current 40 CFR Part 158 data requirements, dermal toxicity studies are required for tau-fluvalinate. The HED Hazard and Science Policy Council (HASPOC) met on August 2, 2012 to discuss whether a subchronic inhalation toxicity study and a 90-day dermal toxicity study are required to support the registered uses of tau-fluvalinate.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Tau-fluvalinate is a type II pyrethroid insecticide/miticide used to control termites and insects in both agricultural and residential settings. Tau-fluvalinate formulations currently include flowable concentrate, liquid, ready- to- use, and impregnated materials. This chemical may be applied as an outdoor general surface spray, perimeter treatment, crack and crevice treatment, and mound treatment around commercial and domestic dwellings. For treatment of landscape ornamentals and nursery uses, tau-fluvalinate may be applied using a broadcast spray, foliar spray, dip treatment, containerized treatment, and basal spray treatment. Greenhouse applications include broadcast, fogger, and bench treatments. For agricultural uses on carrots, and on brassica and cole crops (CA SLNs), tau-fluvalinate may be applied using aerial or ground equipment. Tau-fluvalinate is also labeled for use in the brood chambers of bee hives. Treatments to bee hives are made using impregnated strips. The restricted entry interval (REI) for all crops is 12 hours.

The residential uses include perimeter treatments/outside surfaces, ant mound treatments (spot application) and ready-to-use sprays for pest control on roses, flowers, houseplants, ground covers, ornamentals, shrubs and trees.

In the most recent assessment (R. Travaglini, D321911, 07/25/2005), an oral point of departure (POD) was used to assess acute and chronic dietary for the general U.S. population and short- and intermediate-term inhalation risks. The POD (no observed adverse effect level; NOAEL = 0.5 mg/kg/day) is based on clinical signs seen in at the lowest observed adverse effect level (LOAEL) of 1 mg/kg/day and excessive grooming and bulging eyes seen at the LOAEL (2 mg/kg/day) in the subchronic neurotoxicity study. A POD was not previously selected to assess dermal exposure to tau-fluvalinate because dermal exposures to products containing tau-fluvalinate were expected be self-limiting due to the irritation that occurs as a result of the "pyrethroid reaction" or skin abrasions due to scratching after dermal exposure. The level of concern (LOC) for inhalation risk assessment is a margin of exposure (MOE) < 100.

Tau-fluvalinate is classified as Toxicity Category II by the oral route of exposure, and Toxicity Category III by the dermal route of exposure. Tau-fluvalinate is not irritating to the eye (Toxicity Category III), or skin (Toxicity Category IV), and is not a dermal sensitizer. The principle systemic effects seen in sub-chronic and chronic studies include reduced body weight/body weight gain in dogs and rats, changes in liver weight in dogs and rats, and chronic nephritis in the mouse.

III. INHALATION STUDY WAIVER REQUEST

A. Requirement for the inhalation study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-Chemical Properties:** Tau-fluvalinate has a low vapor pressure of $< 1.0 \times 10^{-7}$ torr and an estimated Henry's Law constant of 1.5×10^{-8} atm-cu m/mole. However, low vapor pressure and/or Henry's law constant does not preclude exposure to aerosolized droplets or particles/dusts.

2. **Use Pattern & Exposure Scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift.

   Tau-fluvalinate formulations currently include flowable concentrate, liquid, ready- to-use, and impregnated materials, and may be applied as an outdoor general surface spray, perimeter treatment, crack and crevice treatment, and an ant mound treatment around commercial and domestic dwellings. For treatment of landscape ornamentals and nursery uses, tau-fluvalinate may be applied using a broadcast spray, foliar spray, dip treatment, containerized treatment, and basal spray treatment. Greenhouse applications include broadcast, fogger, and bench treatments. For agricultural uses on carrots, and on brassica and cole crops, tau-fluvalinate may be applied using aerial or ground equipment. Tau-fluvalinate is also labeled for use in the brood chambers of bee hives. Treatments to bee hives are made using impregnated strips. The restricted entry interval (REI) for all crops is 12 hours. The residential uses include perimeter treatments/outside surfaces, ant mound treatments (spot application) and ready-to-use sprays for pest control on roses, flowers, houseplants, ground covers, ornamentals, shrubs and trees. Currently all

Tau-fluvalinate is a pyrethroid insecticide that acts on the insect's nervous system. The available mammalian toxicity studies also demonstrate typical clinical signs associated with pyrethroid neurotoxicity, including excessive grooming, bulging eyes, abnormal stance, ruffled fur, hyperactivity, salivation, ataxia, muscle spasms, tremors, gait abnormalities, and startle response hyperreaction. Some evidence of nerve degeneration was seen at higher doses in the acute neurotoxicity study. The "pyrethroid reaction" may be one manifestation of tau-fluvalinate's ability to act on nerve endings. The "pyrethroid reaction" occurs during animal feeding studies when dermal contact is made with the feed, unlike the primary dermal irritation assessed in acute or subchronic dermal irritation studies. The severity of the reaction, skin lesions, and subsequent infections, may result in early termination of feeding studies for humane reasons. In humans, the pyrethroid reaction is characterized by tingling sensations and/or severe itching, following contact with tau-fluvalinate.

The rat developmental toxicity study did not show developmental toxicity at the highest dose tested. The rabbit developmental toxicity demonstrated some signs of skeletal variations, including curved tibias and fibulas, only at maternally toxic doses. No reproductive effects of *tau*-fluvalinate were seen. However, the offspring were noted to have tremors in one generation and to have slight body weight decrease in another generation, but these effects occurred at a dose that was also toxic to the parents. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses after *in utero* and/or postnatal exposure to *tau*-fluvalinate in the developmental and reproduction studies. Dose-response relationships are well-characterized and clear NOAELs/LOAELs have been identified. No evidence of carcinogenicity was seen in mice or rats, and there is no concern for mutagenicity.

A Registration Review Scoping Document was recently completed for tau-fluvalinate (D. Drew, D378275, 11/8/2010). HED used the Biological and Economics Analysis Division (BEAD) Label Data System to identify all occupational uses of tau-fluvalinate. An updated occupational inhalation exposure assessment was performed using current ORE policies including revised handler surrogate-exposure data and policy changes for body weight assumptions. Short- and intermediate-term inhalation MOEs range from 1,000 to 21,000) at either baseline or minimum level of personal protection (i.e. PF5R respirator).

Current residential uses include perimeter treatments/outside surfaces, ant mound treatments (spot application) and ready-to-use sprays for pest control on roses, flowers, houseplants, ground covers, ornamentals, shrubs and trees, including a ready-to-use spray formulation that is not restricted to commercial applicators. Although tau-fluvalinate is labeled for use in residential areas, residential handler and post-application exposures have not been previously assessed. Tau-fluvalinate may be applied using a ready-to-use, pump, or hose-end sprayer in residential settings. The residential exposures and risks have been assessed using HED's 2012 Residential SOPs along with policy changes for body weight assumptions. No toxicological dermal endpoints were identified for tau-fluvalinate dermal exposure assessment. Short- and intermediate-term inhalation MOEs range from 97,000 to 1,000,000)

occupational handlers must wear long-sleeved shirt and pants, chemical resistant gloves, shoes and socks as well as NIOSH approved respirators for outdoor and indoor uses at all times.

3. **Margins of Exposure:** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here. For inhalation exposure risk assessment of all durations, an oral POD of 0.5 mg/kg is used for calculating the MOEs. Mixing and loading for hand wand applications led to the highest inhalation exposure to tau-fluvalinate, with an inhalation MOE of 210. There is potential for short- and intermediate-term occupational exposure to tau-fluvalinate during mixing, loading, application, and post-application activities. HED has previously assessed the use of tau-fluvalinate on carrots/brassica, outdoor/indoor ornamentals, outdoor perimeter treatments (structures, buildings, etc), greenhouses and ant mounds for occupational inhalation exposures. Short- and intermediate-term inhalation MOEs range from **1,000 to 21,000**) at either baseline or minimum level of personal protection (i.e. PF5R respirator).

   Occupational exposure assessments of the tau-fluvalinate impregnated strips for beehives, cut flower dipping treatments, and greenhouse foggers have not been previously performed. Occupational exposure resulting from use of the beehive strips is expected to be negligible, as the only potential times for worker contact are during application, when the beehive keeper removes the strips from the containers and places them in the hives, and during removal and disposal of the strips. Since beehives are located outdoors, and the vapor pressure of tau-fluvalinate is low (10^{-7} torr) there is negligible potential for inhalation exposure via vapors. In order to mitigate any potential for dermal exposure, the label requires the use of protective gloves by applicators. Therefore, risk assessments for occupational exposure are not required for the beehive use.

   For the cut flowers dipping treatments, the Agency believes that the mechanically pressurized handgun greenhouse scenario would be a comparable, protective estimate of exposure to tau-fluvalinate through this use. It should be noted that for this scenario the use of a respirator is recommended (i.e., PF5R) in order to achieve an MOE of 1,000.

   In the case of greenhouse fog treatments, occupational risks exposures were not previously assessed due to lack of inhalation exposure data for this use. Potential post-application inhalation exposure in greenhouses is mitigated by the ventilation requirements of the Worker Protection Standard (WPS).

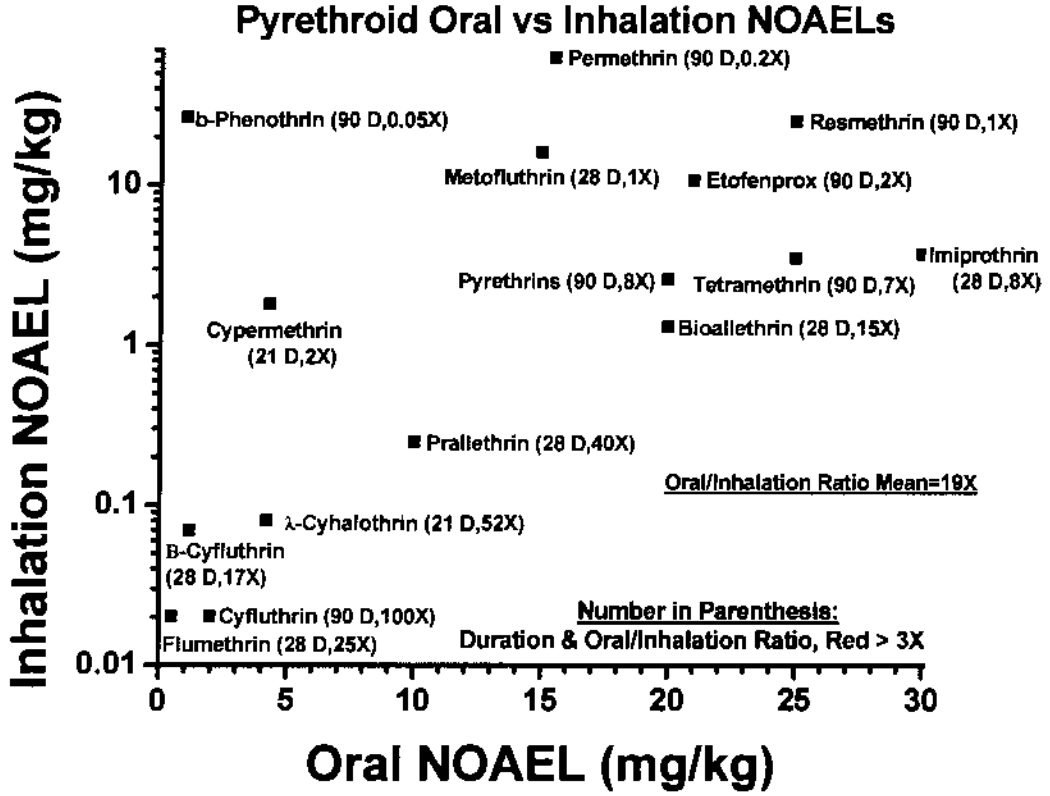
4. **Toxicity:** For tau-fluvalinate, there are no available acute or subchronic inhalation toxicity studies.

For considering a waiver request for inhalation toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on the exposure profile. The toxic MOA for pyrethroids has a rapid temporal pattern with peak time of effect of 1 to 8 hours, depending on the vehicle, vehicle volume, and route of administration. Recovery typically occurs within 24 hours of exposure. When considering the appropriate duration of the required inhalation study for tau-fluvalinate, the team evaluated the sensitivity of respiratory effects in the existing inhalation studies for pyrethroids.

EPA conducted a comparative analysis of repeat-dosing inhalation and oral studies for 15 pyrethroids to determine the relative route-specific toxicity. The inhalation NOAELs were on average 19X lower than the oral NOAELs, indicating that the pyrethroids are more potent following inhalation exposure. Similar results were obtained when comparing the LOAELs. Below is a graphic depiction of this analysis. The inhalation studies for resmethrin and the pyrethrins do not have NOAELs, so the study LOAELs were reported instead.

Of the available pyrethroid inhalation toxicity studies (approximately 15), signs of respiratory toxicity were seen for several chemicals. These signs included: irregular respiration, histopathology in nasal turbinates, decreased lung function, and larynx hyperplasia. In general, respiratory toxicity for the pyrethroids occurred at the same doses as other systemic signs, indicating that the respiratory endpoints were often not more sensitive indicators of toxicity. Inhalation toxicity studies with pyrethrin formulation (57% active ingredient; a.i.), showed hyperplasia in the larynx at 2.56 mg/kg/day while systemic effects of tremors occurred at 26.9 mg/kg/day, although, the formulation's 43% impurity content may be responsible for the respiratory effects.

Although some exceptions are noted, neurotoxicity was the most prominent finding across the pyrethroid toxicity databases. Respiratory effects are not expected to be seen at lower doses than neurotoxicity; tremors are common in the pyrethroid database.



Based on a WOE approach considering of all the available hazard and exposure information for tau-fluvalinate, the HASPOC concluded tbat an acute inhalation study is required. Neurotoxicity has been established as the MOA for the pyrethroids and thus a single-day study is appropriate to assess inhalation toxicity of tau-fluvalinate; a sub-chronic inhalation toxicity study is not needed at this time. The acute inhalation toxicity study should evaluate all parameters as stipulated in the Guideline 870.6200a (acute neurotoxicity study) and the sub-chronic inhalation toxicity (870.3465) studies. It is recommended that the registrant submit the study protocol for Agency review. **However, changes in the use pattern or in the knowledge about the toxicological profile will result in the re-evaluation of this decision by the Agency.**

IV. 90-DAY DERMAL STUDY WAIVER REQUEST

With respect to considering whether a 90-day dermal study is required, the HASPOC used a weight of the evidence approach. This WOE approach considers:

1. **Use pattern & exposure scenarios:** Any application scenario that leads to dermal exposure needs to be considered in the WOE analysis for a dermal toxicology study waiver request. There is potential occupational exposure from mixing/loading tau-

fluvalinate. Exposure is expected to be both short- and intermediate term (1-6 months) duration.

2. **Margins of Exposure (MOEs): No** occupational handler or post-application dermal exposure risks were assessed for tau-fluvalinate because no toxicological dermal endpoints were identified. Dermal exposure to tau-fluvalinate was expected to be self-limiting because of the severe irritation following tau-fluvalinate exposure.

1. Toxicity: A 21-day rabbit dermal toxicity study is available for tau-fluvalinate (NOAEL = 100 mg/kg/day) and skin lesions were seen at doses from 100 to 1,000 mg/kg/day. The lesions may be secondary effects of the "pyrethroid reaction." Systemic effects, such as decreased food consumption and body weight effects were seen at 500 mg/kg/day and above. The 90-day rat dermal toxicity study did not produce a clear NOAEL or LOAEL and was not appropriate for a dermal exposure endpoint. The dermal penetration study was classified as unacceptable/guideline, but estimated the dermal absorption to be 4%. . However, because there is a potential for repeated exposure to tau-fluvalinate longer than 90 days from use patterns, the HASPOC discussed whether a 90-day dermal toxicity study is best suited to assess the longer exposure concerns.

Margins of Exposure (MOEs): No occupational post-application dermal exposure or risk estimates were quantitatively assessed as part of the 2005 RED. No toxicological dermal endpoints were identified for tau-fluvalinate at that time; therefore, a quantitative post-application dermal exposure and risk assessment was not performed. The rationale for lack of quantification of dermal risk was that the dermal exposure should be self-limiting because of the dermal reactions resulting from contact with product. Additionally, each product label bears the personal protective equipment and guidance to avoid contact with skin and instructions to wash the affected area immediately following contact.

The HASPOC concluded, based on a WOE approacb, that a 90-day dermal toxicity study for tau-fluvalinate is not required at this time. This approach considered all of the available hazard and exposure information, particularly that: 1) due to the "pyrethroid effect" a subchronic dermal toxicity study would be inhumane to the test animals; 2) that a dermal study is unlikely to provide a more protective endpoint for risk assessment; and 3) that paresthesia is a local effect and irritation that is likely seen in a dermal toxicity study cannot be used as an endpoint for risk assessment.

V. SUMMARY OF HASPOC RECOMMENDATIONS:

HASPOC concluded that a special acute inhalation study is required. The protocol for this study should include a single exposure via the inhalation route and evaluate parameters specified in both the acute neurotoxicity (870.6200) and the sub-chronic inhalation toxicity (870.3465) studies. This protocol will enable evaluation of toxicity to both the respiratory and nervous system. The protocol must be submitted for Agency review prior to beginning the study.

In the absence of a route-specific inhalation study, a 10X database uncertainty factor should be applied when assessing risk via inhalation exposure. The HASPOC determined that a 90-day dermal toxicity study is not required for tau-fluvalinate at this time.